Tetrahedron Letters
Volume 89, 19 January 2022, 153496

Some unusual transformations of a highly reactive α-bromocaranone

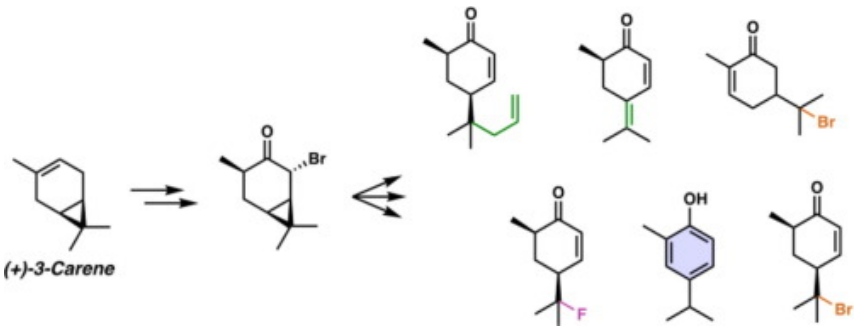
Adrian E. Samkian, Zachary P. Sercel, Scott C. Virgil, Brian M. Stoltz

https://doi.org/10.1016/j.tetlet.2021.153496

Abstract

The facile synthesis of a highly reactive α-bromocaranone from (+)-carene is reported. This intermediate was found to generate diverse chiral building blocks through radical or carbocation mediated cyclopropyl fragmentation reactions in moderate to excellent yields. Furthermore, the formation of an unexpected carvone derivative prompted several control studies that provided mechanistic insight into an unusual transformation. This study not only demonstrates the synthesis of a variety of chiral building blocks but provides insight into the reactivity of keto-halo-cyclopropanes in general.

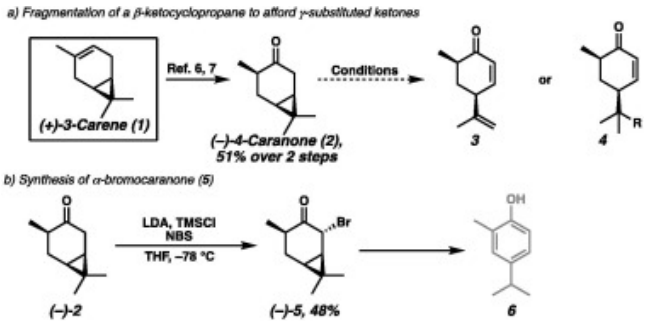
Graphical abstract



Keywords

Carene; Ring fragmentation; Chiral building blocks; Terpenes

The advent of asymmetric catalysis has greatly increased the number and variety of synthetically accessible chiral building blocks [1]. Nevertheless, the syntheses of many natural products and consumer commodities continue to rely on starting materials from the readily available chiral pool and derivatives thereof [2], [3]. As such, strategies for the derivatization of chiral building blocks remain vital in organic synthesis. (+)-3-Carene (**1**, Scheme 1a) is one such building block: the defining dimethylcyclopropane moiety of this molecule coupled with its widespread availability and conveniently rigid structure have made it a popular chiral feedstock [2], [3], [4]. However, among the numerous syntheses beginning from **1**, most feature the presence of the intact dimethylcyclopropane moiety in the target. This is due in part to the lack of mild and selective methods for the fragmentation of the strained ring. Although such fragmentations have been performed on carene (**1**) and related dimethylcyclopropane-containing compounds, the vast majority rely on strongly acidic conditions [5].



Download : Download high-res image (135KB) Download : Download full-size image

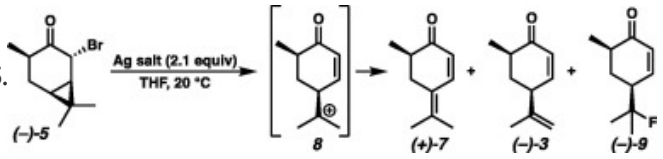
Scheme 1. Synthesis of α-bromocaranone (**5**) from (+)-3-carene.

In the course of a total synthesis effort, we identified the fragmentation of a β-ketodimethylcyclopropane [2] as a valuable transformation for revealing a reactive γ-isopropenyl group [3] from the relatively unreactive, "protected" cyclopropane. Furthermore, we aimed to develop a method to trap the species immediately after ring fragmentation to access the challenging γ-*gem*-dimethyl synthon (**4**). We realized that in order to affect this transformation in a mild and efficient fashion, a synthetic handle would be necessary at the α-position. α-Bromocaranone **5** was selected as a promising model system to study the feasibility of this synthetic transformation due to its straightforward synthesis from carene (**1**) (Scheme 1b).

Hydroboration of commercially available (+)-3-carene (**1**) followed by oxidation afforded (–)-4-caranone (**2**) in modest yields on a >10 g scale [6], [7]. Enolization of (–)-**2** with LiHMDS and direct bromination with NBS led to the production of several inseparable side products [8], however, formation of the silyl enol ether with LDA and TMSCl followed by quenching with NBS led to diminished side product formation, affording (–)-**5** [9]. Although bromide (–)-**5** decomposes rapidly on silica, purification was possible *via* chromatography on neutral alumina. While this compound can be stored for at least several weeks at –15 °C as a solution in benzene, neat samples of bromide (–)-**5** stored at ambient temperature undergo spontaneous, exothermic decomposition to isocarvacrol [6], with the release of HBr, after several hours. Despite the unstable nature of bromide (–)-**5**, it was possible to manipulate neat samples of this intermediate for short periods of time.

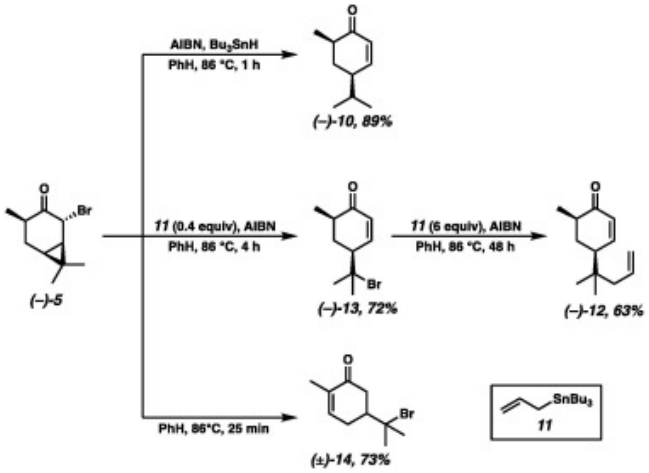
We began by treating bromide (–)-**5** with Ag^I reagents in order to effect a carbocation-mediated fragmentation. Treatment of (–)-**5** with $AgClO_4$ or AgOTf in THF afforded dienone (+)-**7** (Table 1, entries 1 and 2) in modest yields. Trace quantities of the desired compound featuring an isopropenyl group (**3**) were also observed. Attempts to favor the formation of (–)-**3** by performing the reaction in the presence of a bulky base were not successful. The rapid elimination of tertiary carbocation **8** toward (+)-**7** would appear to impede formation of (–)-**3** or trapping with nucleophiles. Despite this, we were surprised to observe tertiary fluoride (–)-**9** as the major product when $AgBF_4$ was used as a Ag^I source (Table 1, entry 3).

Table 1. Ag^I-mediated reactions of **5**.



Entry	Ag salt	Yield (%) 7	Yield (%) 3	Yield (%) 9
1	AgOTf	55%	<5%	–
2	$AgClO_4$	67%	<5%	–
3	$AgBF_4$	10%	5%	35%

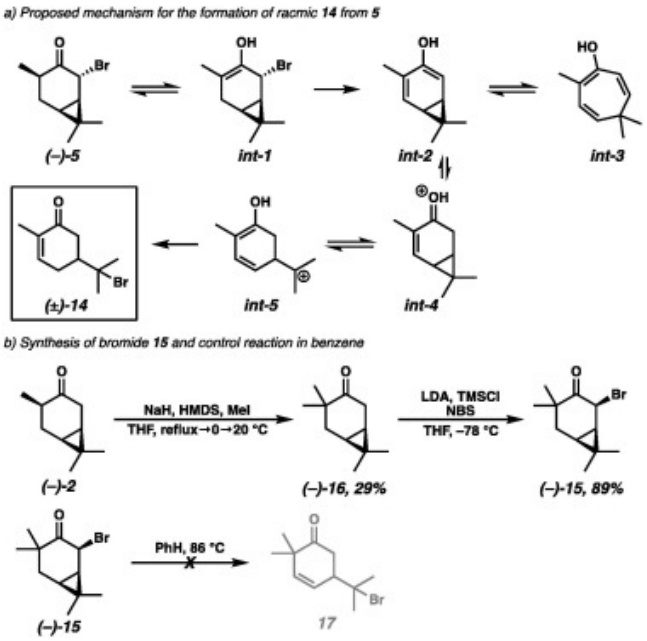
The lack of control observed in carbocation-mediated reactions led us to study radical-mediated fragmentations next. Treatment of (–)-**5** with AIBN and Bu_3SnH afforded isopropyl enone (–)-**10** (Scheme 2) in excellent yield. Allyltributylstannane (**11**) was used in place of Bu_3SnH, in an attempt to prepare the allylated product (–)-**12** [10]. Pleasingly, (–)-**12** was observed, though in moderate yields (<40%), with the tertiary bromide (–)-**13** instead being the major product. Using catalytic amounts of **11** led to high yields of (–)-**13**, which could then be isolated and subjected to similar conditions, albeit with an excess of **11**, to afford the desired allylated species (–)-**12**. It is noteworthy that treatment of dienone (+)-**7** with **11** and AIBN did not afford (–)-**12**, suggesting (+)-**7** is not an intermediate on route to (–)-**12**. The presence of catalytic stannane radicals proved vital for the production of (–)-**13**. Indeed, a control experiment performed by simply heating a solution of (–)-**5** in benzene provided racemic carvone derivative (±)-**14** in high yields, with phenol **6** being observed as a minor product. To explain this surprising divergence in reactivity between (–)-**13** and (±)-**14**, further mechanistic studies were performed.



Download : Download high-res image (121KB) Download : Download full-size image

Scheme 2. Radical mediated cyclopropane fragmentation of **5**.

We initially suspected that the mechanism to form (±)-**14** may be radical mediated, perhaps through the homolysis of the carbon-bromine bond followed by 1,4-HAT. However, such a mechanism would not explain a racemic product. Furthermore, DFT calculations [11], [12], [13] (see SI for details) suggested that the barriers for such a transformation are kinetically inaccessible (>31 kcal/mol). Instead, we propose a polar mechanism (Scheme 3a) that, through elimination of the bromide through enol **int-1**, could afford diene **int-2**. Such a system is precedented to rapidly racemize through an electrocyclic reaction *via* cycloheptatriene **int-3** [14]. Ultimately, **int-2** may be protonated in its keto form **(int-4)**, eventually leading to tertiary cation **int-5**, which is trapped by bromide, affording (±)-**14**.



Download : Download high-res image (215KB) Download : Download full-size image

Scheme 3. Proposed mechanism and control study.

The conversion of (–)-**5** to (±)-**14** is likely catalyzed by HBr formed *via* the decomposition of (–)-**5** to **6**. Interestingly, despite the formation of (–)-**13** requiring longer reaction times (4 h vs. 25 min), carvone derivative (±)-**14** is not observed. Indeed, heating bromide (–)-**5** in PhH in the presence of allylstannane **11** with no radical initiator entirely suppressed the formation of (±)-**14**. We propose that this observation is due to the quenching of HBr by **11**. Another reaction performed with (–)-**5** and bis(tributylstannane), which exists in equilibrium with two tributyltin radicals [15], also suppressed the formation of (±)-**14** whilst producing (–)-**13**, albeit in lower yields. No reaction was observed when (–)-**5** was heated in hexanes, but (±)-**14** was produced rapidly in dioxane or 1,2-dichloroethane with greater quantities of phenol **6**, further implicating a polar mechanism. Finally, control compound (–)-**15** (Scheme 3b), featuring an additional *gem*-dimethyl group, was prepared in two steps from (–)-**2**. This compound was found to be significantly more stable than (–)-**5**, decomposing neither on silica nor spontaneously as a solid compound. Importantly, only clean starting material was observed when (–)-**15** was heated in benzene for extended periods of time, providing further evidence that the reaction leading to (±)-**14** proceeds *via* the mechanism proposed in Scheme 3a.

Over the course of this study, readily available (+)-3-carene was derivatized into an array of useful chiral building blocks through a highly reactive α-bromocaranone as a synthetic branching point. These chiral products are expected to be useful in future synthetic efforts, and we believe that the convenient fragmentation of β-cyclopropyl ketones will also find applications outside of carene-derived systems.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Brian M. Stoltz reports financial support was provided by National Science Foundation. I, Brian M. Stoltz am Editor in Chief of Tetrahedron, the sister journal to which we are submitting.

Acknowledgments

We gratefully acknowledge the National Science Foundation (Grant CHE-1800511) for financial support. Z.P.S. thanks the National Science Foundation for a predoctoral fellowship. The computations presented here were conducted in the Resnick High Performance Computing Center, a facility supported by Resnick Sustainability Institute at the California Institute of Technology. Chiral SFC analysis and preparatory HPLC were performed with instrumentation at the Caltech Center for Catalysis and Chemical Synthesis, a facility of the Beckman Institute at Caltech. High resolution mass spectrometry was performed on an instrument funded by DOW Next Generation Instrument Funds. We thank Alexander Q. Cusumano (Caltech) for assistance with DFT calculations as well as helpful discussions. We thank Dr. Dave VanderVelde (Caltech) for NMR expertise, and Dr. Mona Shahgoli (Caltech) for HRMS data acquisition. This manuscript is dedicated to our friend and colleague Professor Steve Martin in special recognition of his dedication to the *Tetrahedron* family of journals.

Appendix A. Supplementary data

Download all supplementary files Help

The following are the Supplementary data to this article:

Download : **Download zip file (934B)**

Supplementary data 1.

Download : **Download zip file (935B)**

Supplementary data 2.

Download : **Download zip file (924B)**

Supplementary data 3.

Download : **Download zip file (950B)**

Supplementary data 4.

Download : **Download zip file (937B)**

Supplementary data 5.

Download : **Download zip file (934B)**

Supplementary data 6.

Download : **Download zip file (939B)**

Supplementary data 7.

Download : **Download zip file (938B)**

Supplementary data 8.

Download : **Download zip file (945B)**

Supplementary data 9.

Download : **Download zip file (955B)**

Supplementary data 10.

Download : **Download zip file (939B)**

Supplementary data 11.

Download : **Download zip file (942B)**

Supplementary data 12.

Download : **Download Acrobat PDF file (5MB)**

Supplementary data 13.

Download : **Download spreadsheet (11KB)**

Supplementary data 14.

Special issue articles Recommended articles

References

[1] W.A. Nugent, T.V. Rajanbabu, M.J. Burk
Beyond nature's chiral pool: enantioselective catalysis in industry
Science, 259 (1993), pp. 479-483
View PDF CrossRef View Record in Scopus Google Scholar

[2] Z.G. Brill, M.L. Condakes, C.P. Ting, T.J. Maimone
Navigating the chiral pool in the total synthesis of complex terpene natural products
Chem. Rev., 117 (2017), pp. 11753-11795
CrossRef View Record in Scopus Google Scholar

[3] E.M. Carreira, Y.H. Comprehensive
Chirality (2012)

[4] S. Curlat
Recent studies of (+)-3-carene transformations with the retention of the native framework
Chem. J. Mold., 14 (2019), pp. 32-55
CrossRef View Record in Scopus Google Scholar

[5] G. Ohloff, W. Giersch
Säurekatalysierte isomerisierung von α, β-cyclopropyl-oxiranen
Helvetica Chim. Acta, 51 (1968), pp. 1328-1342
CrossRef View Record in Scopus Google Scholar

[6] B. Kilbas, A. Azizoglu, M. Balci
Incorporation of an allene unit into α-pinene via β-elimination
Helvetica Chim. Acta, 89 (2006), pp. 1449-1456
CrossRef View Record in Scopus Google Scholar

[7] A. Kozioł, J. Frątczak, E. Grela, M. Szczepanik, B. Gabryś, K. Dancewicz, S. Lochyński
Synthesis and biological activity of new derivatives with the preserved carane system
Nat. Prod. Res., 34 (2020), pp. 1399-1403
CrossRef View Record in Scopus Google Scholar

[8] X. Zhang, X. Cai, B. Huang, L. Guo, Z. Gao, Y. Jia
Enantioselective total syntheses of pallambins A-D
Angew. Chem. Int. Ed., 58 (2019), pp. 13380-13384
CrossRef View Record in Scopus Google Scholar

[9] Wu K.K.Y., The Diels-Alder reaction in the synthesis of qinghaosu analogues. PhD Thesis, Hong Kong Univerisity of Science and Technology, 2002.
Google Scholar

[10] M. Bruncko, D. Crich, R. Samy
Chemistry of cyclic tautomers of tryptophan: formation of a quaternary center at C3a and total synthesis of the marine alkaloid (+)-Ent-debromoflustramine B
J. Org. Chem., 59 (1994), pp. 5543-5549
CrossRef View Record in Scopus Google Scholar

[11] DFT Calculations Were Carried out with the ORCA Program (See Supporting Information) at the M06-2X/Def2-TZVPP/SMD(Benzene)//M06-2X/Def2-TZVP Level of Theory.
Google Scholar

[12] F. Neese
The ORCA Program System
WIREs Computational Molecular Science, 2 (1) (2012), pp. 73-78
CrossRef Google Scholar

[13] F. Neese
Software Update: The ORCA Program System, Version 4.0
WIREs Comput. Mol. Sci., 8 (1) (2018), p. e1327
View Record in Scopus Google Scholar

[14] E. Marvell
Thermal Electrocyclic Reactions
Elsevier (2012), pp. 283-288
View Record in Scopus Google Scholar

[15] A.G. Davies
Radical chemistry of tin
P.J. Smith (Ed.), Chemistry of Tin, Springer, Netherlands, Dordrecht (1998), pp. 265-289
CrossRef View Record in Scopus Google Scholar

Cited by (0)

View Abstract